UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ALIREZA REZAIE and CHARLES T. ESMON

Appeal No. 2006-0644
Application No. 08/259,321

ON BRIEF[1]

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-3, 5, 7, 8, 14, 15, and 17-21, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment including a heavy chain and a light chain, wherein the antibody or antibody fragment comprise the hypervariable regions of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 which bind an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody and antibody fragment inhibit Protein C activation by thrombin-thrombomodulin, and wherein the

[1] Appellants waived their request for oral hearing. See, paper received February 15, 2006.

antibody and antibody fragment are expressed in bacterial or insect cells or is humanized.

The references relied upon by the examiner are:

Esmon ('638)	5,147,638	Sep. 15, 1992[2]
Esmon ('253)	5,202,253	Apr. 13, 1993
Queen ('101)	5,530,101[3]	Jun. 25, 1996
Queen ('861)	WO 90/07861[4]	Jul. 26, 1990

Morrison, "Transfectomas Provide Novel Chimeric Antibodies," Science, Vol. 229, pp. 1201-1207 (1985)

D'Angelo et al. (D'Angelo), "Relationship between Protein C Antigen and Anticoagulation Activity during Oral Anticoagulation and in Selected Disease States ," Journal Clinical Investigation, Vol. 77, pp. 416-425 (1986)

Stearns et al. (Stearns), "The Interaction of Ca2+-dependent Monoclonal Antibody with the Protein C Activation Peptide Region," J. Biol. Chem., Vol. 263, No. 2, pp. 826-832 (1988)[5]

GROUNDS OF REJECTION

Claims 1-3, 5, 7, 8, 14, 15 and 17-21 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on any one of '253, '638, D'Angelo or Stearns in combination with any one of Morrison, '861 or '101.

Claims 1-3, 5, 7, 8, 14, 15 and 17-21 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

[2] We note that the examiner incorrectly identifies the date of this references as "April 13, 1992." Answer, page 3.

[3] We note that the examiner incorrectly identifies the Patent No. for this reference as "5,553,101." Answer, page 2. The examiner, however, refers to the correct Patent No. in the statement of the rejection. Answer, page 3.

[4] We note that the examiner incorrectly identifies the Publication No. for this reference as WO "90107861." Appellants, however, refer to the correct Publication No. Brief, page 4.

[5] We note that the examiner incorrectly identifies the Journal and Volume of this reference as "New England Journal of Medicine, Vol. 262." Appellants, however, refer to the correct Journal and volume. Brief, page 4.

over claims 1-3 of United States Patent No. 5,202,253 in view of Morrison or '861.[6]

We reverse.

CLAIM INTERPRETATION

Claim 1 on appeal is drawn to "[a] recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment including a heavy chain and a light chain. . . ." Regarding the term "antibody fragment," appellants' specification refers to Fab and scFv fragments. See e.g., specification, pages 7 and 17.

The antibody or antibody fragment of claim 1 comprise "the hypervariable regions of the monoclonal antibody produced by the hybridoma deposited - with the American Type Culture Collection as ATCC No. HB 9892. According to appellants' specification "monoclonal antibody, HPC-4, [was] deposited with the American Type Culture Collection, Rockville, MD, on November 2, 1988, and assigned ATCC No. HB 9892. . . ."

The antibody or antibody fragment of claim 1 binds "an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody and antibody fragment inhibit Protein C activation by thrombin-thrombomodulin. . . ."

[6] While appellants incorrectly identify the claims under rejection (compare Brief, pages 4 and 16 with Answer, page 4, and Final Rejection, page 3), appellants identify the Queen reference as Queen, WO 90/07861. Brief, pages 4 and 16. Since we are unable to identify which of the two Queen references identified as prior art in the Answer, were applied in this ground of rejection, we will proceed on the basis of appellants' understanding that the rejection was based on the combination of '253 in view of Morrison or Queen WO 90/07861.

In addition, claim 1 includes a process limitation "wherein the antibody and antibody fragment . . . [is] expressed in bacterial or insect cells or is humanized."

DISCUSSION

Obviousness:

The examiner relies on '253, '638, D'Angelo and Stearns in the alternative. While each reference discloses the HPC-4 antibody, we find that Stearns and '253 provide the most detailed description of the antibody.

According to Stearns (page 826, second column, third full paragraph), a Ca^{2+} dependent monoclonal antibody to human protein C was isolated and designated HPC4. Stearns teaches (id.) that "[i]n the presence of Ca^{2+}, this antibody binds to protein C, but not activated protein C...." Stearns also teaches (bridging paragraph, pages 826-827), that a Ca^{2+}-binding site is present on the antibody and "is necessary for high affinity antigen binding." According to Stearns (page 831, column 2, first full paragraph), the metal ion-binding site in the antibody mediates Ca^{2+}'s "stabilization of the antigen-HPC4 complex." Stearns, however, does not teach the location of the Ca^{2+} binding site in the HPC4 antibody. Stated differently, Stearns does not disclose whether the Ca^{2+} binding site is present in one or more of the CDR regions, one or more of the variable regions, on some part of the constant region of the antibody, or some combination of the preceding.

The '253 patent that the HPC-4 monoclonal antibody "was deposited with the American Type Culture Collection 12301 Parklawn Drive, Rockville, Md. 20852, on Nov. 2, 1988, and has been assigned ATCC No. HB 9892." '253, column 6, lines 17-26. Accord, appellants' specification, pages 3, lines 14-15, "HPC-4 is disclosed and claimed in U.S. Patent No. 5,202,253 [('253)] to Esmon, et al." According to '253 (column 2, lines 62-65), the HPC-4 antibody is Ca^{2+} dependent and "specifically binds to a specific twelve peptide sequence (E D Q V D P R L I D G K) in the activation region of the Protein C of non-bovine origin...," only in the presence of calcium (column 3, lines 47-48). More specifically, '253 discloses (column 6, lines 61-68),

> [w]hen calcium binds to the metal ion binding site, the monoclonal antibody becomes significantly more receptive to binding to the peptide. When a metal ion is not bound to the metal ion binding site of the monoclonal antibody, the antigen binding site is relatively unreceptive to binding the antigen. Accordingly, antibody-antigen binding may be controlled by varying the metal ion concentration in the media surrounding the antibody.

'253, however, does not disclose the location of the Ca^{2+} binding site in the HPC-4 antibody. At best, '253 suggests that one experiment is to localize the metal binding region of HPC-4. See, '253, column 11, lines 13-15, "[t]he metal binding region of HPC-4 can be localized using limited proteolysis techniques to produce small fragments of the antibody." In this regard, '253 recognizes (column 12, lines 18-23), that the metal binding region of HPC-4 may now reside in a single stretch of amino acids, e.g., the region may exist on "segments of both the heavy and light chain. . . ."

The '638, and D'Angelo references do not make up for the lack of teaching as to the location of the metal binding region of HPC-4. Similarly, Morrison, '861 and '101, relied upon by the examiner in the alternative to teach the methodology for producing humanized antibodies, does not make up for the lack of a teaching in any of the primary references as to the location of the metal binding region of HPC-4.

Why is it necessary to know the location of the metal binding region of HPC-4? According to appellants' claimed invention, the monoclonal antibody is calcium dependent and is derived from the HPC-4 antibody. As we understand the examiner's rejection, the combination of references relied upon teach a humanized HPC-4 antibody. According to appellants' specification (page 15), "[a] humanized antibody is one in which the antigen-recognizing sites, or complementarity-determining hypervariable regions (CDRs) are of non-human origin, whereas all other regions including the framework regions (FRs) of variable domains are products of human genes." Stated differently, as can be seen from the secondary references relied upon by the examiner, in general, to humanize the murine HPC-4 antibody taught by the primary references, the CDR regions would be removed and cloned into the framework region of a human antibody. Therefore, unless the metal binding region of the HPC-4 antibody existed in the CDR region, the HPC-4 antibody would no longer possess the ability to bind Ca^{2+}. Absent the ability to bind Ca^{2+}, the

humanized antibody, would not be calcium dependent and therefore would not teach all of the limitations of appellants' claimed invention.

Consistent with the discussion set forth above, appellants assert (Brief, page 6), "one of skill in the art could not have predicted that it was merely the amino acid sequence forming the variable region of the HPC-4 murine antibody that was responsible for the unique protein-calcium binding specificity of the antibody." In response, the examiner finds (Answer, page 5), appellants' argument to be "mere assertions, unsupported by fact." According to the examiner, the HPC-4 antibody's "unique binding specificity[is] imparted by the unique amino acid sequence of its hypervariable regions. . . ." However, as discussed above, there is no evidence on this record that it is the hypervariable region of the HPC-4 antibody that is responsible for the antibodies' calcium dependency.

As set forth in In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991):

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under [35 U.S.C.] § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

On this record, we find that the examiner failed to meet her burden of providing the evidence necessary to establish that a person of ordinary skill in

the art at the time of appellants' invention would have had a reasonable expectation of success in obtaining a humanized calcium dependent HPC-4 antibody, by following the teachings of the combination of references relied upon. In the absence of a reasonable expectation of success, one is left with only an "obvious to try" situation which is not the standard of obviousness under 35 U.S.C. § 103. See In re O'Farrell, 858 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). Accordingly, we reverse the rejection of claims 1-3, 5, 7, 8, 14, 15 and 17-21 under 35 U.S.C. § 103.

Double Patenting:

According to the examiner (Answer, page 4), "[c]laims 1-3, 5, 7-8, 14-15 and 17-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of US, Patent No. 5,202,253 in view of Morrison or Queen, for reasons of record in previous office actions." As we understand the examiner's Final Rejection, the rationale for rejecting the claims under the judicially created doctrine of obviousness-type double patenting is the same as was applied to the rejection of claims under 35 U.S.C. § 103. See Paper mailed March 31, 1999, page 3, paragraph 8, "[t]he rejection of claims 1-3, 5, 7-8, 14-15 and 17-21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,202,253 in view of Morrison or Queen is maintained. Please see the arguments below [which address the rejection under 35 U.S.C. § 103]."

Accordingly, we reverse this rejection for the same reasons set forth in our discussion of the rejection under 35 U.S.C. § 103. Specifically, we find that the examiner failed to meet her burden of providing the evidence necessary to establish that a person of ordinary skill in the art at the time of appellants' invention would have had a reasonable expectation of success in obtaining a humanized calcium dependent HPC-4 antibody, by following the teachings of the combination of references relied upon.

OTHER ISSUES

We note, however, that '253 discloses (column 11, lines 33-36), "HPC-4 cDNA can be cloned and sequenced by methods known to those skilled in the art. cDNA can be prepared from hybridoma cell line HPC-4 (ATCC number 9892). . . ." In addition, '253 discloses (column 12, lines 3-10),

> chimeric cDNA can ... be cloned into an appropriate expression vector, such as Baculovirus according to the procedures described in Summers, M.D. and G.E. Smith, "A manual of methods for Baculovirus vectors and insect cell culture procedures"... Expression of the recombinant gene can be achieved by the methods described therein.

On first impression, it would appear to us that expressing the HPC-4 antibody in an insect or bacterial cell would not suffer the problems associated with humanizing the antibody as discussed above, since the nucleic acid sequence of the antibody would not be modified when expressed in insect or bacterial cells, unlike the situation when the antibody is humanized.

According to appellants (Brief, page 14), "[e]ven though the claimed subject matter is an antibody, the antibody cannot be made except by expression

of the nucleotide sequence, [therefore] the antibody cannot be obvious from the naturally occurring antibody." In this regard, appellants' assert (id.), to find otherwise would be in conflict with our appellant reviewing courts' holding in In re Deuel, 51 F.3d 1552 34 USPQ2d 1210 (CAFC 1995). As we understand appellants' arguments (see Brief, pages 7-10 and 14), Deuel, see also In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), stand for the proposition that it is per se error to rely upon so-called methodology in determining the patentability of claims directed to a product. We note, however, that since the decisions in Bell and Deuel, our appellate reviewing court has made it clear that there are no per se rules of obviousness or nonobviousness. In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) ("reliance on per se rules of obviousness is legally incorrect"). Accord, In re Brouwer, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

Since there are no per se rules of obviousness or nonobviousness, each case must be decided upon the facts in evidence in that case. See In re Cofer, 354 F.2d 664, 667, 148 USPQ 268, 271 (CCPA 1966)("[n]ecessarily it is facts appearing in the record, rather than prior decisions in and of themselves, which must support the legal conclusion of obviousness under 35 U.S.C. § 103"); and Ex parte Goldgaber, 41 USPQ2d 1172, 1176 (Bd. Pat. App. & Int. 1995) ("each case under 35 U.S.C § 103 is decided on its own particular facts").

As discussed above, '253 discloses (column 11, lines 33-36) that "HPC-4 cDNA can be cloned and sequenced by methods known to those skilled in the art. cDNA can be prepared from hybridoma cell line HPC-4 (ATCC number 9892)

. . . ." In addition, '253 discloses (column 12, lines 3-10), chimeric cDNA can be cloned into an appropriate expression vector. Therefore, not only does '253 teach the exact antibody from which appellants' derive their hypervariable region, '253 discloses that the cDNA encoding this antibody can be isolated from the hybridoma that produces this antibody. There is no evidence or argument on this record that the claimed hypervariable region of appellants' claim 1 would be different from that obtained following the disclosure of '253. Accordingly, we do not find appellants' argument persuasive.

Prior to any further action, we encourage the examiner to take a step back and reconsider appellants' claimed invention in view of the available prior art, to determine whether the claimed invention is free of any prior art teaching the expression of the HPC-4 antibody in insect cells, or bacterial cells.

In this regard, we note that during prosecution the examiner applied the '253 reference as an anticipatory reference. See e.g., Paper mailed April 29, 1997, page 12. The examiner, however, withdrew the anticipation rejection in view of appellants' claimed amendment, which in relevant part, modified the last clause of claim 1 as follows - "wherein the antibody and antibody fragment are expressed in bacterial or insect cells or [contains human amino acid sequence] is humanized." See Paper received June 8, 1998, page 2. According to the examiner (Paper mailed August 31, 1998), the anticipation rejection "is withdrawn in view of [appellants'] amendment to the claims to include the limitation 'humanized.'" As we understand the June 8, 1998 amendment, as well as, claim 1 now before us on appeal, the "humanized" limitation is an alternative

limitation 'humanized.'" As we understand the June 8, 1998 amendment, as well as, claim 1 now before us on appeal, the "humanized" limitation is an alternative limitation. As we understand claim 1, the antibody or antibody fragment can be expressed in bacterial or insect cells; or it can be humanized.

Accordingly, we encourage the examiner to take a step back and reconsider the full scope of appellants' claimed invention to determine whether the claimed invention is free of art.

REVERSED

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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